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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/203,078	12/01/98	ZHANG S	INRP:081

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EXAMINER	
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ART UNIT	PAPER NUMBER
1648	17

DATE MAILED:
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/203,078	Applicant(s) ZHANG ET AL.	
	Examiner Shanon A. Foley	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *30-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The examiner of your application has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1648, Examiner Foley.

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-29 in Paper No. 16 is acknowledged.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 29 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 31 and 43 of copending Application No. 09/880,609. Although the conflicting claims are not identical, they are not patentably distinct from each other because the adenovirus obtained by the process claimed in the instant application is indistinguishable from the adenovirus contained in the composition in application '609.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 9, 11-18, 20, 21, 30-39, 41-47, 50-53, 61-64, 66-69, 71-74, 78-80, 86-89 of U.S. Patent No. 6,194,191. Although the conflicting claims are not identical, they are not patentably distinct from each other because although the method of preparing the adenovirus in the patent does not require that the producer cells be infected at a particular phase in the cell cycle, a cell culture comprises cells in all phases of the cycle. Therefore, the patent inherently covers cells that are infected at every specific phase, even though it is not specifically claimed.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 30-43 of this application conflict with claims 30-43 of Application No. 09/880,609. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 30-43 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 30-43 of copending Application No. 09/880,609. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 4, 20, 23, and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is drawn to producer cells being seeded using a homogeneous pool of cells. How are the homogeneous cells aiding the seeding of the producer cells? Is the homogeneity of the cells referring to cell type and/or synchronicity of the cell phase? If the producer cells are a homogeneous pool of cells in the same cycle, it is suggested that applicant amend the claim to reflect this concept.

Claim 4 states that the producer cells are perfused "at least a portion of the time". Are the producer cells being perfused in step a) of claim 1, and not step b), or vice versa? Or are the cells being perfused off and on in steps a) and b) of claim 1? It cannot be discerned what is meant by this phrase in the claim since the specification defines perfusion as a continuous process, see page 31, line 11.

Claim 20 recites the limitation "producer cells" in line 1. There is insufficient antecedent basis for this limitation in the claim. For examining purposes, this claim is being treated as if it depends from claim 1. However, this does not relieve applicant of the burden of response to this rejection.

Claim 23 recites the limitation "recombinant gene" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 25 recites the limitation "said promoter" in line 1. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 26-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 26 is drawn to lysing producer cells "by means other than freeze-thaw". While the specification on page 35, line 23 –page 37, and page 42, lines 9-12, discusses a variety of methods to lyse cells, including freeze-thaw, the specification does not reasonably support the specific exclusion of the freeze-thaw method. Although Table 2 on page 37 does identify this method as "not scalable, not recommended for large scale manufacturing", the table also identifies other methods as "scalability concerns". Although the specification reasonably conveys a variety of methods for lysing cells, the specification is not seen as reasonably

conveying the concept of "any method except freeze-thaw", which is now the scope of the subject matter of these claims. This affects dependent claims 27 and 28.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 9, and 13-24, and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Huyghe et al. (C44).

The claims are drawn to a process of preparing a p53 recombinant adenovirus by preparing a culture of 293 cells, and infecting the cells between mid-log and stationary phase and, harvesting the adenovirus from the culture by a variety of chromatographic means, including ion exchange chromatography, and putting the harvested virus into a pharmaceutical composition.

Huyghe et al. teaches a method for purifying a recombinant adenovirus encoding p53 from 293 cells by a variety of chromatographic techniques, including ion exchange, see the abstract, first paragraph under "materials and methods", and the section bridging pages 1407-1408. Since the cells were infected at 50-60% confluency, the cell culture would inherently comprise cells at every phase in the cell cycle at the time of infection and therefore anticipate infecting cells at a particular phase.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Huyghe et al. as applied to claims 1, 2, 9, and 13-24, and 26 above, and further in view of Kraft et al. (Archives of Virology 1978. 57 (3): 243-54. Abstract only.)

Although this claim is indefinite for reasons discussed above, in the interest of compact prosecution, it is assumed that the claim is drawn to the producer cells being homogeneous pool of cells of the same type and phase. Huyghe et al. does not teach this concept. However, Kraft et al. correlates the production of CELO adenovirus with the S phase in synchronized cultures. Therefore, it would have been obvious for one of ordinary skill in the art to infect a homogeneously synchronized cell culture at the optimum time in the cell cycle to increase virus yields. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation in producing the claimed invention by the routine optimization technique taught by Kraft et al. Therefore, the invention is seen as prima facie obvious, absent unexpected results.

Claims 4-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huyghe et al. as applied to claims 1, 2, 9, and 13-24, and 26 above, and further in view of Garnier et al. (C26) or Perrin et al. (C73).

The claims are drawn perfusing the producer cells to maintain a certain level of glucose in the culture. Huyghe et al. does not teach perusing the 293 cells. However, in the art of virus production, perfusion cultures have been used for large-scale growth of cells for virus production. For example, Perrin et al. and Garnier et al. teach scale-up adenovirus growth using medium replacement for controlling glucose concentrations for improved virus yields. It would have been within the skill of the ordinary artisan to scale-up culture using a perfusion system for the advantages of large-scale production of virus as suggested by Perrin et al., and to optimize the rate of medium replacement and glucose level for the advantage of improving virus yield taught by Garnier et al. Therefore, the invention is seen as prima facie obvious, absent unexpected results.

Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Huyghe et al., Garnier et al., and Perrin et al. as applied to claims 1, 2, 4-7, 9, 13-24, and 26 above, and further in view of Graham et al. (C32).

The claim is drawn to lysing the producer cells by detergent lysis. Huyghe et al., Garnier et al., nor Perrin et al. teach lysing cells with detergent. Graham et al. teaches that using a 5% sodium deoxycholate will disrupt cells without disrupting adenovirus virions, see page 119. Therefore, it would have been prima facie obvious to use a detergent as an alternative method to lyse adenovirus-infected cells.

Claims 8 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huyghe et al., Kraft et al., Garnier et al., Perrin et al., or Graham et al. as applied to claims 1-7, 9, 13-24, 26 and 27 above, and further in view of Zhang et al. (6,143,290).

The claims are drawn to a step of cell settling before infection and the p53 gene under the control of a particular promoter.

None of the previous references teach the specific promoter, but Zhang et al. teaches a method for expressing an adenovirus encoding p53 that is under the control of an SV40 promoter. Since all of the promoters listed in claim 25 are used conventionally for gene expression in adenovirus, all would be obvious alternatives to the promoter used by Zhang et al. to one of ordinary skill in the art at the time the invention was made.

Zhang et al. also teaches that the 293 cells were inoculated 24 hours prior to viral transfection into flasks, see column 18, lines 12-18. In the tissue culture art, it is standard practice to let cells settle and recover at least a few hours before manipulation. One of ordinary skill in the art at the time the invention was made would have been motivated to get the producer cells in optimum condition before transfection, i.e. letting them settle. Immediately burdening the cells with more stress from the virus to be transfected would decrease cell survival and lead to low virus yields. Therefore the invention as a whole would have been prima facie obvious to the ordinary artisan, absent unexpected results.

Claims 10-12 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huyghe et al., Kraft et al., Garnier et al., Perrin et al., Graham et al., or Zhang et al. as applied to claims 1-9 and 13-27.

The claims are drawn to specific producer cell numbers to be plated prior to transfection and particular characteristics of the harvested adenovirus

All of the references teach various methods of purifying recombinant adenoviruses. Although none of the references teach specific cell numbers to be plated, this number would be a

very subjective determination by one of ordinary skill in the art to be based on many different factors, such as the type of cell, what condition the cells are in before plating, how fast the cells divide, ect. All of these factors and others must be taken into account before seeding. Too many cells will result in clumping and the virus will not have access to as many cells as it would with fewer cells. Too few cells would result in poor cell condition from lack of other cell contact and eventually cell death (depending on the type of cell). Therefore, it would be prima facie obvious for one of ordinary skill in the art to determine the appropriate cell number required for each situation encountered.

Although none of the references teach a harvested adenovirus with the characteristics listed in claim 29, all of the references teach various methods for improving the quantity and/or purity of the recombinant adenovirus obtained. Therefore, it would be obvious for one of ordinary skill in the art at the time the invention was made to test for any one of the properties listed to ensure a good yield of adenovirus.

The invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon A. Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on 7:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley/SAF
September 7, 2001

James C. Housel
JAMES HOUSEL 9/10/01
SUPERVISORY PATENT EXAMINER
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